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EXAMINER	
JANSSEN, SHANNON L	

ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
03/31/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/537,588	PASCHKE, MATTHIAS	
	Examiner	Art Unit	
	SHANNON JANSSEN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21, 24-30, and 32-35* is/are pending in the application.

4a) Of the above claim(s) *2,10-21 and 24-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9 and 32-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 June 2005 and 02 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-21, 24-30, and 32-35 are currently pending. The amendment received December 16, 2009 amended claims 4 and 9. The amendment received February 24, 2011 canceled claim 31 and added claims 32-35. Claims 2, 10-21 and 24-30 have been withdrawn and claims 1, 3-9, and 32-35 are currently under consideration.

Election/Restrictions

Applicant's elected Group I, claims 1-9, with traverse in the reply filed on June 22, 2009 and further clarified on July 7, 2009.

Claims 10-21 and 24-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Inventions, there being no allowable generic or linking claim.

Applicant's elected species of (a) a first fusion protein fragment: phage coat protein (claim 4) and a second fusion protein fragment: a protein encoded by a cDNA (claim 3), (b) interaction domain for a first protein: a leucine zipper domain (claim 6) and interaction domain for a second protein: a leucine zipper domain (claim 6), and (c) a translocation sequence for a first fusion protein: a Sec-dependent sequence (claim 7) and a translocation sequence for a first fusion protein: a Tat-dependent sequence (claim 8) **without** traverse in the reply filed on June 22, 2009 and further clarified in the response filed on July 7, 2009.

Claim 2 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to German application 10256669.0, filed December 4, 2002. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. It is noted that applicant cannot rely upon the foreign priority papers to overcome a rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. The present application also claims status as a National Stage entry of PCT/EP2003/013709, filed December 4, 2003.

Withdrawn Objections

The objection to Claim 31 is withdrawn in view of the claim amendments.

Withdrawn Rejections

The rejection of Claim 31 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the claim amendments.

Invention as claimed

The present invention is drawn to a protein mixture comprising: a) at least a first fusion protein comprising: i) a protein or protein fragment, ii) an interaction domain and iii) a protein translocation sequence which effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic membrane in an essentially unfolded state, and b) at least a

second fusion protein comprising: i) a protein or protein fragment, ii) an interaction domain and iii) a protein translocation sequence which effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic membrane in an essentially folded state, wherein the interaction domain of the first fusion protein can bind to those of the second fusion protein, and various embodiments.

Maintained Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-7, 9, and 32-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Crameri et al. (Display of biologically active proteins on the surface of filamentous phages: a cDNA cloning system for selection of functional gene products linked to the genetic information responsible for their production, 1993, Gene, vol 137, pp 69-75). Modifications to the rejection were necessitated by the claim amendments.

Regarding present **claims 1 and 32-35**, Crameri et al. teach a) a first fusion protein comprising: i) PIII (i.e.: a protein or protein fragment; see p 70, col 2, para 2), ii) a Jun Leucine zipper interaction domain (see p 70, col 1, para 4, col 2, para 2), and iii) a pelB translocation signal sequence (i.e.: a Sec-dependent protein translocation sequence which effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic membrane in an essentially unfolded state; see p 70, col 1, para 4, col 2, para 2, Fig. 1), and b) a second

fusion protein comprising: i) a cDNA from a cDNA library (i.e.: protein or protein fragment), ii) a Fos Leucine zipper interaction domain (see p 70, col 1, para 4, col 2, para 2,and iii) a pelB signal sequence (i.e.: a protein translocation sequence which effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic membrane), wherein the interaction domain of the first fusion protein can bind to those of the second fusion protein (throughout document, see particularly p 70, col 1, para 4, Fig. 1).

Note: the limitations regarding folding state (e.g.: that the fusion protein is translocated in an essentially folded or unfolded state) are not given patentable weight because they are interpreted as a process of making and not the end product currently claimed (e.g.: a specific structure that would provide different folding requirements is not presently in the claims). Additionally, the recitations of "effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic membrane in an essentially folded state," "wherein the second fusion protein is in an essentially folded state when translocated through the cytoplasmic membrane," "wherein the protein translocation sequence targets the second fusion protein to a protein translocation pathway which translates the second fusion protein in an essentially unfolded state…," "wherein the second fusion protein is in an essentially folded state when expressed…," and "wherein the second fusion protein is translocated through the cytoplasmic membrane in an essentially folded state" is interpreted as functional language and is not given patentable weight because the said functional recitation does not appear to add additional structural limitations to the instant claimed product. See MPEP § 2106, II, C and 2111.02 II.

Regarding present **claim 3**, Crameri et al. teach a second fusion protein comprising a cDNA from a cDNA library (see p 70, col 1, para 4, Fig. 1).

Regarding **claims 4-5**, Crameri et al. teach the M13 pIII phage coat protein (see p 70, col 2, para 2).

Regarding **claim 6**, Crameri et al. teach the first fusion protein with a Jun leucine zipper interaction domain and the second fusion protein with a Fos leucine zipper interaction domain (see p 70, col 2, para 2).

Regarding **claim 7**, Crameri et al. teach wherein the first fusion protein comprises the pelB signal sequence (i.e.: Sec-dependent signal sequence; see p 70, col 1, para 4, col 2, para 2, Fig. 1).

Regarding **claim 9**, Crameri et al. teach covalent linking of the Jun and Fos leucine zippers (i.e.: the first fusion protein is covalently bound to the second fusion protein through the leucine zippers; see p 70, col 1, para 4, Fig. 1).

Therefore, the teachings of Crameri et al. anticipate present claims 1, 3-7, and 9.

Response to Arguments

Applicant's arguments filed February 24, 2011 have been fully considered but they are not persuasive for the following reasons. Applicants' arguments are presented in Italics.

Applicants assert that the functional recitations of claim 1 do provide structural limitations (Reply, p 16).

In response, it is noted that there is no specific common core structure listed in the specification as corresponding to effecting translocation through the cytoplasmic membrane in an essentially folded state (e.g.: the sequences which effect translocation in an essentially folded state do not share a common core structure). In the absence of a specific core structure corresponding to the functional limitation, the limitation does not limit the structure. Applicants

do not currently have a specific structure (e.g.: a specific sequence) in the claims that would provide specific folding requirements. A "stretch of amino acids," with no specific amino acids recited, does not constitute a specific core structure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham **v.** John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3-9, and 32-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crameri et al. (Display of biologically active proteins on the surface of filamentous phages: a cDNA cloning system for selection of functional gene products linked to the genetic information responsible for their production, 1993, Gene, vol 137, pp 69-75) and Weiner et al. (US Patent 6,335,178, granted January 1, 2002), as evidenced by Wu et al. (Membrane targeting and translocation of bacterial hydrogenases, 2000, Arch Microbiol, Vol 173, pp 319-324). Modifications to the rejection were necessitated by the claim amendments.

Regarding present **claims 1 and 32-35**, Crameri et al. teach a) a first fusion protein comprising: i) PIII (i.e.: a protein or protein fragment; see p 70, col 2, para 2), ii) a Jun Leucine zipper interaction domain (see p 70, col 1, para 4, col 2, para 2), and iii) a pelB translocation signal sequence (i.e.: a Sec-dependent protein translocation sequence which effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic membrane in an essentially unfolded state; see p 70, col 1, para 4, col 2, para 2, Fig. 1), and b) a second fusion protein comprising: i) a cDNA from a cDNA library (i.e.: protein or protein fragment), ii) a Fos Leucine zipper interaction domain (see p 70, col 1, para 4, col 2, para 2,and iii) a pelB signal sequence (i.e.: a protein translocation sequence which effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic membrane), wherein the interaction domain of the first fusion protein can bind to those of the second fusion protein (throughout document, see particularly p 70, col 1, para 4, Fig. 1).

Note: the limitations regarding folding state (e.g.: that the fusion protein is translocated in an essentially folded or unfolded state) are not given patentable weight because they are interpreted as a process of making and not the end product currently claimed (e.g.: a specific structure that would provide different folding requirements is not presently in the claims). Additionally, the recitations of "effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic membrane in an essentially folded state," "wherein the second fusion protein is in an essentially folded state when translocated through the cytoplasmic membrane," "wherein the protein translocation sequence targets the second fusion protein to a protein translocation pathway which translates the second fusion protein in an essentially unfolded state…," "wherein the second fusion protein is in an essentially folded state when

expressed…," and "wherein the second fusion protein is translocated through the cytoplasmic membrane in an essentially folded state" is interpreted as functional language and is not given patentable weight because the said functional recitation does not appear to add additional structural limitations to the instant claimed product. See MPEP § 2106, II, C and 2111.02 II.

Regarding present **claim 3**, Crameri et al. teach a second fusion protein comprising a cDNA from a cDNA library (see p 70, col 1, para 4, Fig. 1).

Regarding **claims 4-5**, Crameri et al. teach the M13 pIII phage coat protein (see p 70, col 2, para 2).

Regarding **claim 6**, Crameri et al. teach the first fusion protein with a Jun leucine zipper interaction domain and the second fusion protein with a Fos leucine zipper interaction domain (see p 70, col 2, para 2).

Regarding **claim 7**, Crameri et al. teach wherein the first fusion protein comprises the pelB signal sequence (i.e.: Sec-dependent signal sequence; see p 70, col 1, para 4, col 2, para 2, Fig. 1).

Regarding **claim 9**, Crameri et al. teach covalent linking of the Jun and Fos leucine zippers (i.e.: the first fusion protein is covalently bound to the second fusion protein through the leucine zippers; see p 70, col 1, para 4, Fig. 1).

Although Crameri et al. teach first and second fusion proteins covalently bound, Crameri et al. do not teach a second fusion protein comprising a Tat-dependent translocation sequence.

Regarding present **claims 1 and 8**, Weiner et al. (as evidenced by Wu et al., where the Mtt pathway and the Tat pathway are the same pathway; see abstract, p 319, col 2) teach a Tat-

dependent translocation sequence that transports folded proteins through the cytoplasmic membrane (see Weiner et al., col 1, 2, 10, and examples 1-5).

It would have been obvious to one of skill in the art to use the Tat-dependent translocation sequence taught by Weiner et al. in the fusion protein mixture taught by Crameri et al. One would have been motivated to do so to take advantage of the ability of the Tat pathway to transport folded proteins. One would have had a reasonable expectation for success because Weiner et al. teach that the translocation sequences translocate functional folded proteins through the cell membrane (see col 1, 2, 10, and col 35, para 2 - col 36, para 1). Therefore, the teachings of Crameri et al. and Weiner et al. render the present invention to be prima facie obvious.

Response to Arguments

Applicant's arguments filed February 24, 2011 have been fully considered but they are not persuasive for the following reasons. Applicants' arguments are presented in Italics.

Applicants assert that the functional recitations of claim 1 do provide structural limitations (Reply, p 18).

In response, it is noted that there is no specific common core structure listed in the specification as corresponding to effecting translocation through the cytoplasmic membrane in an essentially folded state (e.g.: the sequences which effect translocation in an essentially folded state do not share a common core structure). In the absence of a specific core structure corresponding to the functional limitation, the limitation does not limit the structure. Applicants do not currently have a specific structure (e.g.: a specific sequence) in the claims that would provide specific folding requirements. A "stretch of amino acids," with no specific amino acids

recited, does not constitute a specific core structure. A "stretch of amino acids," with no specific amino acids recited, does not constitute a specific core structure.

Applicants assert there would be no motivation to combine the references (Reply, p 19+).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, all the references teach proteins with translocation sequences relating to folding and transportation into the periplasmic space or extracellular matrix. In addition, Weiner et al. state:

"Such translocation offers a unique advantage over current methodologies for protein purification. Because the composition of culture medium can be manipulated, and because the periplasm contains only about 3% of the proteins of gram negative bacteria, expressed proteins which are translocated into the extracellular medium or into the periplasm are more likely to be expressed as functional soluble proteins than if they were translocated to cellular membranes or to the cytoplasm. Furthermore, translocation to the periplasm or to the extracellular medium following protein expression in the cytoplasm allows the expressed protein to be correctly folded by cytoplasmic enzymes prior to its translocation, thus allowing retention of the expressed protein's biological activity." (See col 10).

Therefore, one of skill in the art would have been motivated to utilize the Tat sequence taught by Weiner et al. in order to take advantage of the benefits taught by Weiner et al.

Further, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute one known element (i.e.: the Tat translocation sequence taught by Weiner et al.) for another known element (i.e.: the PelB translocation sequence taught by Crameri et al.)

because it would have yielded the predictable result of a folded protein. See KSR International Co. v. Teleflex Inc., USPQ2d 1385 (U.S. 2007).

In addition, it is noted that the instant claims are currently directed to a protein mixture not a cell containing the protein mixture. Applicants' arguments appear to be directed to the intended use of the product rather than the product as instantly claimed.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a cell containing the proteins, which are transported out of the cell) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Applicants are claiming a product, not a method of using the product.

Applicants assert that Choi et al. teach an in vitro system while the present application is an in vivo system (Reply, p 20).

Contrary to applicants' assertions, the instant claims do not recite an in vivo system. The present claims recite a protein mixture. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., an in vivo system) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants assert that Choi et al. do not teach the binding of two proteins (Reply, p 20).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the fusion proteins are transported via different mechanisms to the same compartment) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Applicants are respectfully reminded that the instant claims are directed to a product, a protein mixture, which is not required to be present in a cell, and not a method of making or using the product.

In addition, the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). See MPEP § 2145 I.

Applicants appear to argue that Choi et al. teaches away from the present invention (Response, p 20).

In response to applicants' arguments that Choi et al. teach away from the claimed invention, disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ

423 (CCPA 1971). See MPEP § 2123. In addition, Choi et al. was cited to show that cell free protein expression systems were known in the art.

Claims 1, 3-9, and 32-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crameri et al. (Display of biologically active proteins on the surface of filamentous phages: a cDNA cloning system for selection of functional gene products linked to the genetic information responsible for their production, 1993, Gene, vol 137, pp 69-75) and Georgiou et al. (US Patent 7,419,783, filed November 5, 2002, with benefit to provisional applications 60/404944, filed August 21, 2002, and 60/337452, filed November 5, 2001). Modifications to the rejection were necessitated by the claim amendments.

Regarding present **claims 1 and 32-35**, Crameri et al. teach a) a first fusion protein comprising: i) PIII (i.e.: a protein or protein fragment; see p 70, col 2, para 2), ii) a Jun Leucine zipper interaction domain (see p 70, col 1, para 4, col 2, para 2), and iii) a pelB translocation signal sequence (i.e.: a Sec-dependent protein translocation sequence which effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic membrane in an essentially unfolded state; see p 70, col 1, para 4, col 2, para 2, Fig. 1), and b) a second fusion protein comprising: i) a cDNA from a cDNA library (i.e.: protein or protein fragment), ii) a Fos Leucine zipper interaction domain (see p 70, col 1, para 4, col 2, para 2,and iii) a pelB signal sequence (i.e.: a protein translocation sequence which effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic membrane), wherein the interaction domain of the first fusion protein can bind to those of the second fusion protein (throughout document, see particularly p 70, col 1, para 4, Fig. 1).

Note: the limitations regarding folding state (e.g.: that the fusion protein is translocated in an essentially folded or unfolded state) are not given patentable weight because they are interpreted as a process of making and not the end product currently claimed (e.g.: a specific structure that would provide different folding requirements is not presently in the claims). Additionally, the recitations of "effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic membrane in an essentially folded state," "wherein the second fusion protein is in an essentially folded state when translocated through the cytoplasmic membrane," "wherein the protein translocation sequence targets the second fusion protein to a protein translocation pathway which translates the second fusion protein in an essentially unfolded state…," "wherein the second fusion protein is in an essentially folded state when expressed…," and "wherein the second fusion protein is translocated through the cytoplasmic membrane in an essentially folded state" is interpreted as functional language and is not given patentable weight because the said functional recitation does not appear to add additional structural limitations to the instant claimed product. See MPEP § 2106, II, C and 2111.02 II.

Regarding present **claim 3**, Crameri et al. teach a second fusion protein comprising a cDNA from a cDNA library (see p 70, col 1, para 4, Fig. 1).

Regarding **claims 4-5**, Crameri et al. teach the M13 pIII phage coat protein (see p 70, col 2, para 2).

Regarding **claim 6**, Crameri et al. teach the first fusion protein with a Jun leucine zipper interaction domain and the second fusion protein with a Fos leucine zipper interaction domain (see p 70, col 2, para 2).

Regarding **claim 7**, Crameri et al. teach wherein the first fusion protein comprises the pelB signal sequence (i.e.: Sec-dependent signal sequence; see p 70, col 1, para 4, col 2, para 2, Fig. 1).

Regarding **claim 9**, Crameri et al. teach covalent linking of the Jun and Fos leucine zippers (i.e.: the first fusion protein is covalently bound to the second fusion protein through the leucine zippers; see p 70, col 1, para 4, Fig. 1).

Although Crameri et al. teach first and second fusion proteins covalently bound, Crameri et al. do not teach a second fusion protein comprising a Tat-dependent translocation sequence.

Regarding present **claims 1 and 8**, Georgiou et al. teach a Tat-dependent translocation sequence that transports the folded proteins it is fused to through the cytoplasmic membrane (Throughout document, see particularly columns 1,2 and examples 7 and 8).

It would have been obvious to one of skill in the art to use the Tat-dependent translocation sequence taught by Georgiou et al. in the fusion protein mixture taught by Crameri et al. One would have been motivated to do so to take advantage of the ability of the Tat pathway to transport folded proteins. One would have had a reasonable expectation for success because Georgiou et al. teach that the Tat-dependent translocation sequences translocate functional folded proteins through the cell membrane (throughout document, see particularly examples 7 and 8). Therefore, the teachings of Crameri et al. and Georgiou et al. render the present invention to be prima facie obvious.

Response to Arguments

Applicant's arguments filed February 24, 2011 have been fully considered but they are not persuasive for the following reasons. Applicants' arguments are presented in Italics.

Applicants assert that the functional recitations of claim 1 do provide structural limitations (Reply, p 18).

In response, it is noted that there is no specific common core structure listed in the specification as corresponding to effecting translocation through the cytoplasmic membrane in an essentially folded state (e.g.: the sequences which effect translocation in an essentially folded state do not share a common core structure). In the absence of a specific core structure corresponding to the functional limitation, the limitation does not limit the structure. Applicants do not currently have a specific structure (e.g.: a specific sequence) in the claims that would provide specific folding requirements. A "stretch of amino acids," with no specific amino acids recited, does not constitute a specific core structure. A "stretch of amino acids," with no specific amino acids recited, does not constitute a specific core structure.

Applicants assert there would be no motivation to combine the references (Reply, p 19+).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, all the references teach proteins with translocation sequences relating to folding and transportation into the periplasmic space or extracellular matrix. In addition, Weiner et al. state:

"Such translocation offers a unique advantage over current methodologies for protein purification. Because the composition of culture medium can be manipulated, and because the

periplasm contains only about 3% of the proteins of gram negative bacteria, expressed proteins which are translocated into the extracellular medium or into the periplasm are more likely to be expressed as functional soluble proteins than if they were translocated to cellular membranes or to the cytoplasm. Furthermore, translocation to the periplasm or to the extracellular medium following protein expression in the cytoplasm allows the expressed protein to be correctly folded by cytoplasmic enzymes prior to its translocation, thus allowing retention of the expressed protein's biological activity." (See col 10).

Therefore, one of skill in the art would have been motivated to utilize the Tat sequence taught by Weiner et al. in order to take advantage of the benefits taught by Weiner et al.

Further, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute one known element (i.e.: the Tat translocation sequence taught by Weiner et al.) for another known element (i.e.: the PelB translocation sequence taught by Crameri et al.) because it would have yielded the predictable result of a folded protein. See KSR International Co. v. Teleflex Inc., USPQ2d 1385 (U.S. 2007).

In addition, it is noted that the instant claims are currently directed to a protein mixture not a cell containing the protein mixture. Applicants' arguments appear to be directed to the intended use of the product rather than the product as instantly claimed.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a cell containing the proteins, which are transported out of the cell) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Applicants are claiming a product, not a method of using the product.

Applicants assert that Choi et al. teach an in vitro system while the present application is an in vivo system (Reply, p 20).

Contrary to applicants' assertions, the instant claims do not recite an in vivo system. The present claims recite a protein mixture. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., an in vivo system) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants assert that Choi et al. do not teach the binding of two proteins and that the mechanism of transport of the fusion proteins is important (Reply, pp 20-21).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the fusion proteins are transported via different mechanisms to the same compartment) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Applicants are respectfully reminded that the instant claims are

directed to a product, a protein mixture, which is not required to be present in a cell, and not a method of making or using the product.

In addition, the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). See MPEP § 2145 I.

Applicants appear to argue that Choi et al. teaches away from the present invention (Response, p 20).

In response to applicants' arguments that Choi et al. teach away from the claimed invention, disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). See MPEP § 2123. In addition, Choi et al. was cited to show that cell free protein expression systems were known in the art.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Future Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHANNON JANSSEN whose telephone number is (571)270-1303. The examiner can normally be reached on Monday-Friday 10:00AM-7:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amber D. Steele/
Primary Examiner, Art Unit 1639

Shannon L Janssen
SLJ